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A RANDOMISED CONTROL TRIAL ON EFFECT OF VITAMIN D IN STROKE IN A TERTIARY CARE HOSPITAL OF SOUTHERN ODISHA

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Abstract

Introduction: Stroke has many different aspects, depending on the type, demography, and severity. Vitamin D insufficiency may bear an association with acute stroke. Vitamin D deficiency is frequent in people who have been paralysed due to a stroke. Vitamin D, a neurosteroid with receptors found throughout the brain, plays a role in neuroprotection via a variety of mechanisms.

Objective Role of vitamin D in stroke and its outcome.

Materials And Methodology: A total of 325 stroke patients were included, with 130 instances of hypovitaminosis being randomised into two groups, GROUP A and B, each of which had 65 cases. Vitamin D levels and the Scandinavian Stroke Scale (SSS) score were measured before and after treatment. **Intervention:** In addition to conventional stroke treatment and physiotherapy, GROUP A got a single IM injection of 6 Lac IU of Vitamin D, while GROUP B (control) received standard stroke treatment and physiotherapy.

Design of The Study: randomized control trial in a Tertiary Care Teaching hospital

STUDY PERIOD: FEBRUARY 2020 – JANUARY 2022

A follow-up was scheduled after three months, and the outcome was assessed using SSS at that time .

Observation And Result: The average age at the time of the stroke was 67.61±2.39 years, and the majority of the patients (77.23%) were male. At the time of admission, 85 percent of stroke patients had hypovitaminosis D. Following treatment, there was a rise of serumvitamin D level of 12.09 ng/ml in GROUP A (p value < 0.001) and a decrease of 1.47 ng/mlin GROUP B at the end of 3 months.

Result: There was significant improvement in SSS Score in GROUP A(49.12%) in comparison to GROUP B (11.44%).

Conclusion: There was significant improvement in disability in stroke cases with normalization of the serum vitamin D level following supplementation. As it's deficiency is easy to screen for and inexpensive to treat, screening for Vitamin D deficiency may be done routinely in stroke.

Keywords: stroke, SSS, hypovitaminosis D

Introduction

The World Health Organization (WHO) definition of stroke is, " rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin"[1]. Thus the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis. The clinical manifestations of stroke are highly variable because of the complex anatomy of the brain and its vasculature[2]. The pathological background for stroke may either be ischemic or hemorrhagic disturbances of the cerebral blood circulation. Risk factors are multiple.

In the recent years, due to the increase in the development of economy and change in demography, there is a shift towards lifestyle-related chronic non-communicable diseases and stroke is one of them, which causes serious long term neurological disability and contributes to morbidity and mortality.

The incidence of stroke in entire world population is 0.22 per 1000 people. According to World Health Organization (WHO) report, approximately around 15million people are struck by stroke every year, of which around one third die and another one third have permanent disability[3]. Due to the increasing elderly population worldwide, stroke prevalence and incidence are becoming more common, lethal, debilitating and costly. Therefore, the need of the hour emphasizes on neuroprotection.

The neuroprotective agents like therapeutic hypothermia, hyperacute magnesium therapy, high dose human albumin, GABA agonists, calcium channel blockers, glutamate antagonists, down-regulators of the nitric oxide signal transduction, free radical scavengers and antioxidants, are the ones that have been most extensively studied without much promising outcome[4].

Multiple literature and articles have suggested the deficiency of Vitamin D to have deleterious effects on the modifiable risk factors as well as non-modifiable risk factors. They have been implicated as a neuro-hormone and some role in neuro-protection as well. It is unique because it is the only endogenously synthesized vitamin that also acts as a hormone.

Besides its main role in calcium homeostasis and bone metabolism, the vitamin D endocrine system is found to have a wide range of fundamental biologic functions in inhibition of cell growth, immunomodulation and cell differentiation[5]. Vitamin D is a fat soluble secosteroid. The component circulating in blood is 25hydroxy Vitamin D, major portion (40-50%) of which is derived from skin. The active component, 1,25hydroxy vitamin D (Calcitriol), is transported in the blood to many target organs by Vitamin D Binding Protein (VDBP). It serves as a chemical messenger that transmits rapid responses and regulates the transcription of various genes in the target cells. Individual tissues produce their own Vitamin D3 in a tissue specific fashion. Pathophysiological mechanisms remain speculative, but several possible biological mechanisms might explain the association of low 25 hydroxy-Vitamin D with stroke.

Lower vitamin D levels can induce brain damage and cognitive and functional impairment. Vitamin D deficiency has been associated with morphological brain changes, motor impairments, and memory and learning impairments in animal models. Additionally, numerous studies have indicated that vitamin D deficiency is associated with accelerated bone resorption and reduced bone mineral density in stroke patients. In addition, low 25(OH)D levels may contribute to pro-atherosclerotic changes of vascular smooth muscle cells, endothelial dysfunction and increased macrophage to foam cell formation.

High dose oral vitamin D supplementation produced short-term improvement in endothelial function in stroke patients with well-controlled baseline blood pressure. Finally, low 25(OH) D levels are known to influence macrophage and lymphocyte activity in atherosclerotic plaques and to promote chronic inflammation in the artery wall.

AIM AND OBJECTIVE:

1. To find the baseline serum Vitamin D levels in various types of stroke patients
2. To find out the effect of Vitamin D supplementation in patients of stroke with vitamin D insufficiency and the quality of life during recovery.

Materials And Methodology

This Randomized Control Trial study was carried out in the Department of General Medicine over two years. The study protocol was approved by the Ethical Committee of M.K.C.G medical college & Hospital, Berhampur.

STUDY DESIGN : Randomized Control Trial

SETTING: in a tertiary care teaching hospital

PERIOD OF STUDY: FEBRUARY 2020 TO JANUARY 2022

Inclusion Criteria

1. Evidence of stroke on CT / MRI scan imaging
2. First onset episode of stroke.
3. Presentation within seven days of onset of stroke.
4. Age more than or equal to 35 years.
5. Were ambulatory prior to the stroke.

Exclusion Criteria

1. Patients receiving supplements of calcium and/ or vitamin D.
2. Patients who have been thrombolysed.
3. Bone diseases

4. Multiple organ involvement and impairment
5. Cognitive and mental changes
6. Recurrent history of stroke
7. Pregnancy
8. Hepatic and renal impairment
9. Endocrinal disorders
10. Smoking
11. Steroid therapy
12. Previous history of fractures
13. Malignancy
14. Autoimmune disorders
15. History of acute and chronic inflammatory diseases
16. Trauma
17. Death of patient during the follow-up period
18. History of myocardial infarction within the last three months

Material And Method

A total number of 325 stroke patients were enrolled in this study. Out of them, 123 were hemorrhage and 202 were ischemia. After considering the inclusion and exclusion criteria, 155 cases were excluded. Vitamin D estimation was done at the time of presentation and SSS calculated. 170 cases met the criteria and were included in this study, of which 40 had normal vitamin D values. 130 cases of HYPOVITAMINOSIS D remained and were randomized for the study. They were divided into two groups, GROUP A and B, comprising of 65 cases each. Baseline vitamin D levels and Scandinavian Stroke Scale (SSS) score was recorded. In GROUP A, along with conventional stroke treatment and physiotherapy, a singleIM injection of 6 Lac IU of Vitamin D was administered to the patients. On the other hand, GROUP B received the conventional treatment and physiotherapy, and served as the control. Sample size of 130 with 65 cases in each of the intervention and the control group taking anticipated mean of 65±4.08 in intervention group and 63 in control group with alpha 0.05 and power as 80%.
Cases were followed up after three months. (Figure-1)

Data Collection

Initial diagnosis of stroke was done on the clinical basis, followed by confirmation of the diagnosis with the aid of radiological imaging (CT / MRI). General examination and thereby calculation of Scandinavian Stroke Scale (SSS) was done at time of admission. Blood samples were taken at the time of admission and after three months to measure the serum levels of 25 hydroxy Vitamin D level by electro chemiluminescence binding assay Technique. VITAMIN D status was evaluated based on US Endocrine society norms with serum 25-hydroxy vitamin D NORMAL: ≥ 30 ng/ml , DEFICIENT : ≤ 20 ng/ml and INSUFFICIENT : 21-29 ng/ml. Since Vitamin D values are not always whole numbers, the insufficient group is to be between > 20 and< 30ng/ml.

All relevant data were recorded in a Master Chart in the Microsoft Excel Program 2010. Data analysis was done with the help of computer using standard SPSS software package (Statistics Products Services Solutions) version 17.0.

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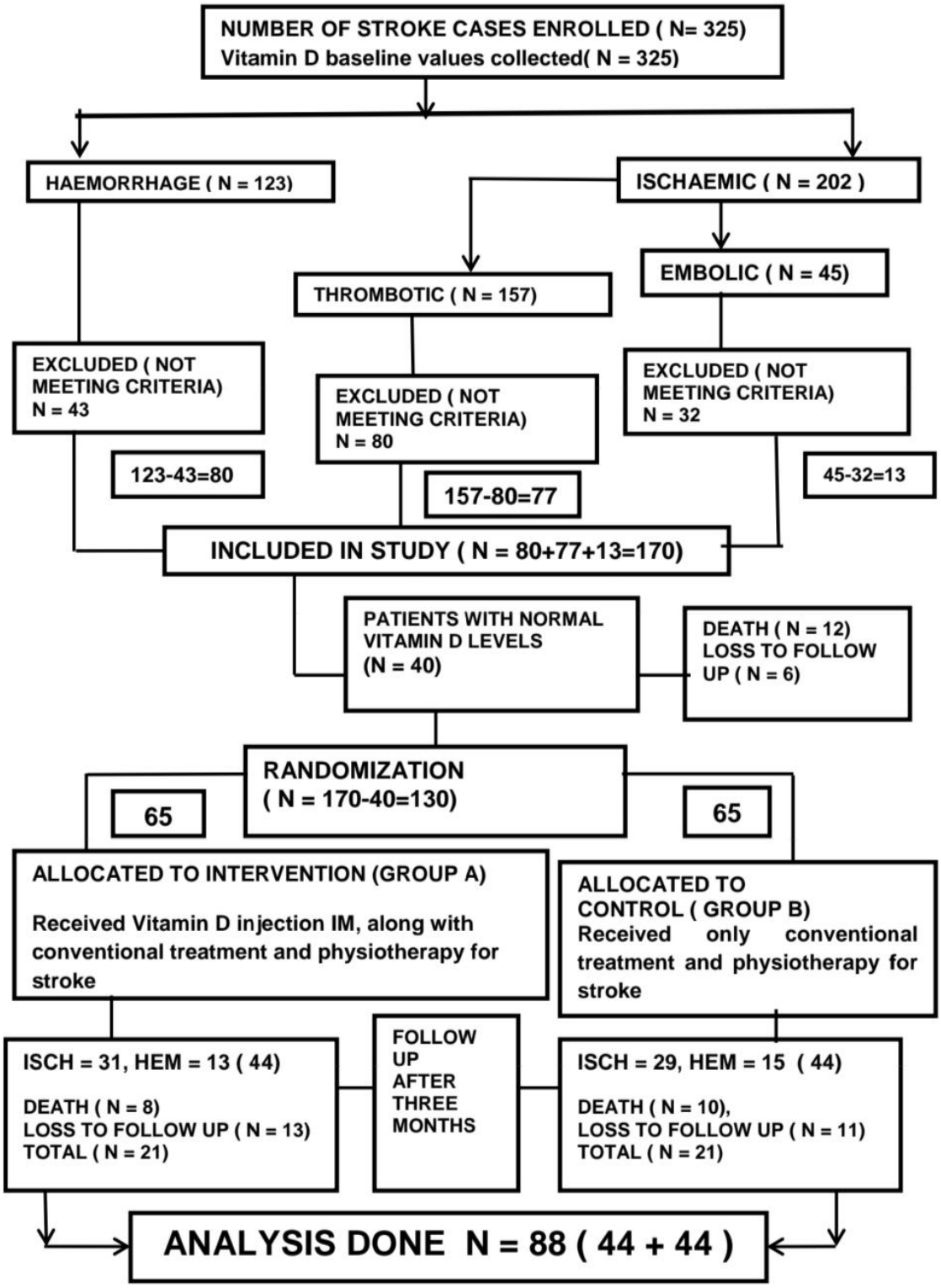
FIGURE -1: STUDY DESIGN - FLOW CHART



Observation

TABLE 1: NUMBER OF STROKE PATIENTS

TYPES OFSTROKE n = 325		NUMBER	PERCENTAGE
ISCHAEMIC	Thrombotic	157	48.3
202 (62.15%)	Embolic	45	13.85
HAEMORRHAGIC		123	37.85
123 (37.85%)	TOTAL	325	100%

In this study, the number of total stroke patients were 325. Out of that, 123 (7.84%) were of haemorrhagic and 202 (62.15%) were ischaemic. Under the ischemic variety, 157 (48.3%) were of thrombotic type and 45 (13.85%) were of embolic type. (Table-1)

TABLE 2: VITAMIN D STATUS AT TIME OF ADMISSION IN STROKE CASES(n = 325)

VITAMIN D LEVEL	LEVELS (in ng/ml)	NUMBER OF CASES	% age	MEAN ± SD
DEFICIENCY	≤20	94	28.92	15.62 ± 2.57
INSUFFICIENCY	> 20 - <30	185	56.92	24.51 ± 2.53
NORMAL	≥ 30	46	14.15	34.34 ± 2.63

Vitamin D status was divided into 3 subtypes, of which the maximum number of patients 185 (56.92%) fell into the insufficiency category. It was followed by 94 (28.92%) cases who were of Vitamin D deficiency category. So, in total, 279 cases (85.84%) had insufficient levels of vitamin D. Only 46 (14.15%) stroke patients had normal Vitamin D levels at time of admission.(Figure -2)

FIGURE 2: VITAMIN D STATUS AT TIME OF ADMISSION IN STROKECASES(n = 325)

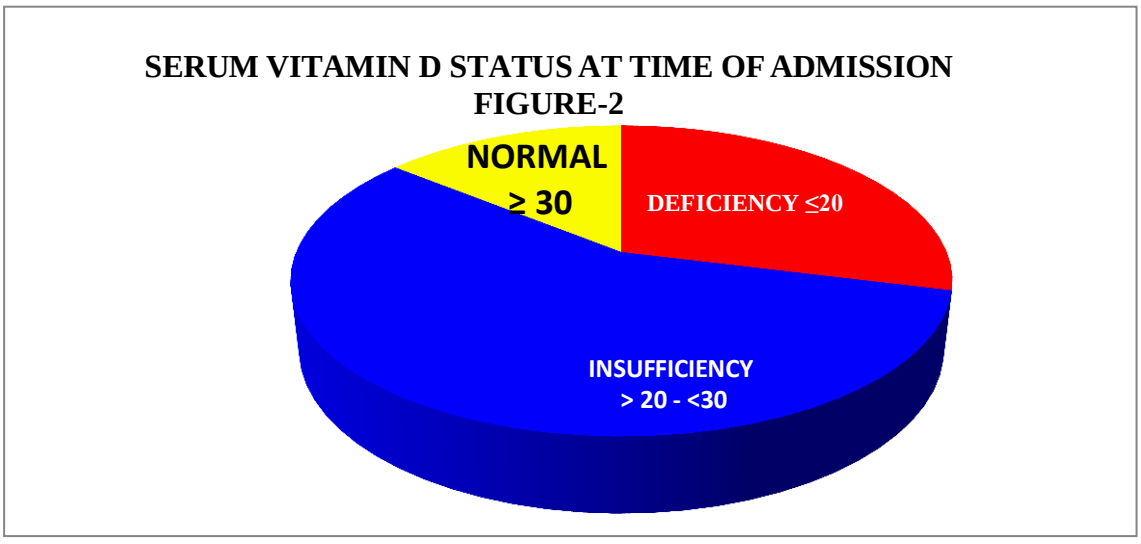


TABLE 3: COMPARISON OF VITAMIN D LEVELS IN BOTH GROUPS(PRE AND POST TREATMENT)

GROUP (N =88)	AT ADMISSION Mean value (in ng/ml)	AFTER 3 MONTHS Mean value (in ng/ml)	DIFFERENCE	Test Statistic, P value
GROUP A (N = 44)	21.64	33.73	12.09	T=24.899, p<0.001
GROUP B (N = 44)	21.55	20.08	- 1.47	T =1.643, p=0.108

44cases each were assessed as GROUP A and GROUP B. The initial serum Vit D level was 21.64ng/ml and 21.55ng/ml, respectively in GROUP A and GROUP B. At the end of 3 months, serum Vit D levels were reassessed in both groups and the values were 33.73 and 20.08, respectively. This is depicted in the bar graph.(Figure3)

FIGURE 3 : COMPARISON OF VITAMIN D LEVELS

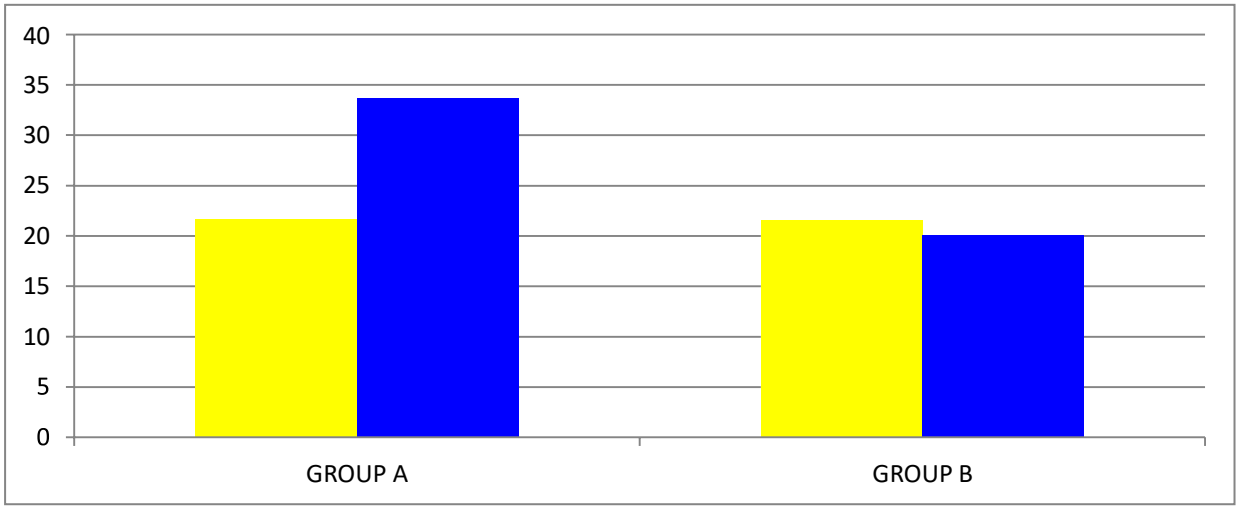


TABLE 4:Comparison Of SSS scores in both groups (pre and post treatment)

GROUP (N = 88)	SSS AT ADMISSION (MEAN)	SSS AFTER 3 MONTHS (MEAN)	DIFFERENCE IN SCORES	% age improvement in SSS SCORES	T value, p value
GROUP A (N = 44)	25.63	38.22	12.59	49.12%	T=19.67, p<0.001
GROUP B (N =44)	28.4	31.65	3.25	11.44%	T=6.33, p<0.001

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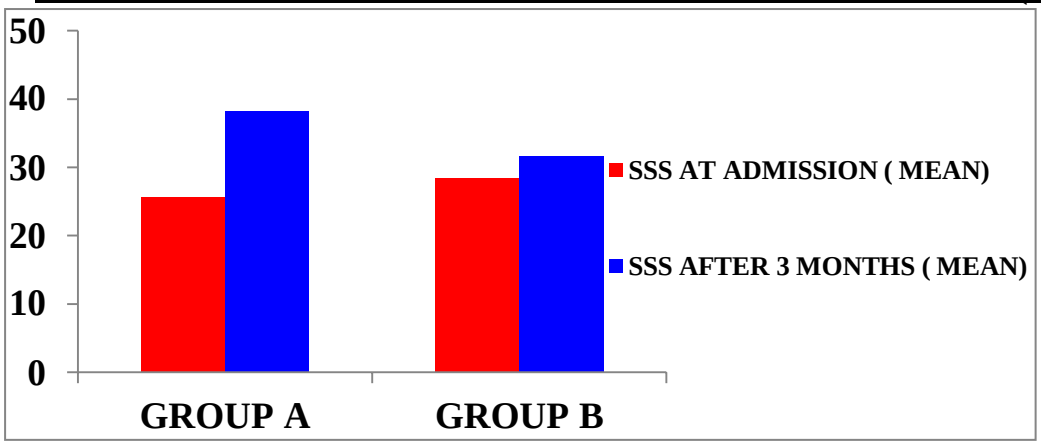
The Scandinavian Stroke Scale score was assessed in both groups at the time ofadmission and reassessed after 3 months. At the time of admission, SSS score was 25.63 and28.4, respectively in GROUP A and GROUP B (CONTROL), and it was 38.22 and 31.65,respectively at the end of 3 months. This is depicted in the cone diagram.(figure 4)

FIGURE 4: COMPARISON OF SCANDINAVIAN STROKE SCALES (N = 88)



Discussion

This study had the following outcomes:The number of total stroke patients was 325. Out of that, 202 (62.15%) were ischaemic and 123 (37.84%) were hemorrhagic, the ratio being 1.64: 1. Under the ischemic variety, 157 (48.3%) were of thrombotic type and 45 (13.85%) were of embolic type **[TABLE 1]**. **Banerjee et al** had similar observation like our study. They suggested thatbased on neuroimaging findings, recent studies have determined the stroke subtypes and the ratio of cerebral infarct to hemorrhage range as 1.86:1-2.21:1. Hence, cerebral hemorrhage is proportionately much higher in the Eastern Indian community than in Western countries, where the ratio of infarct to hemorrhage is 5:1[6].Study by **Kamalakannan et al**[7]showed that the crude stroke prevalence in different parts of India ranged from 44.29 to 559/100,000 persons during the past two decades.

In this study, 325 cases of stroke were subgrouped into 4 groups, where maximum number was noticed in the 66-80 years age group i.e. 151 cases (46.46%). Mean age of presentation at the time of stroke was 67.6 ±12.39 years which is similar to the study by **Sridharan et al**[8] who showed it to be 67 years..

The mean value was calculated to be 23.06 ± 6.205 ng/ml. In our study, about 85% cases of stroke had Hypovitaminosis D. Vitamin D status was divided into 3 subtypes, of

which the maximum number of patients 185 (56.92%) fell into the insufficiency category. It was followed by 94 (28.92%) cases that were of Vitamin D deficiency category. So, in total, 279 cases (85.84%) had insufficient levels of vitamin D. Only 46 (14.15%) stroke patients had normal Vitamin D levels at time of admission [**TABLE 2, FIGURE 1].**

Wajda et al had also found about 88% of the stroke patients to be in the range of moderate and severe vitamin D deficiency [9].

The initial serum vitamin D level was 21.64 ng/ml and 21.55 ng/ml, respectively in GROUP A and GROUP B. At the end of 3 months, levels were reassessed in both groups andthe values were 33.73 and 20.08, respectively. There was a rise of serum vitamin D level of

12.09 ng/ml in GROUP A and a decrease of 1.47 ng/ml in GROUP B at the end of 3 months. The p value was significant (< 0.001) in GROUP A. In GROUP B (CONTROL), the decrease in mean serum vitamin D value was probably due to increased demand during the recovery phase and non-supplementation of exogenous vitamin D **[TABLE 3, FIGURE 2].**

The Scandinavian Stroke Scale score was assessed in both groups at the time of admission and reassessed after 3 months**.** At the time of admission, SSS score was 25.63 and 28.4, respectively in GROUP A and GROUP B (CONTROL), and it was 38.22 and 31.65, respectively at the end of 3 months. There was 49.12% increase in GROUP A and 11.44% in GROUP B (CONTROL) in the SSS score and this difference was found to be statistically significant (p< 0.001) **[TABLE 4, FIGURE 3]. Narsimhan et al**[10] also had reported increase in mean SSS after three months which was statistically significant (p<0.001).

In 2013, **the Vitamin D council**[11], in its statement declared that Vitamin D deficiency is an important global problem with significant association to stroke. It suggested many groups to do further studies into the association between Vitamin D and stroke and the pathogenesis behind it. The **Ludwigshafen Risk and Cardiovascular Health (LURIC) Study**[12] conducted from 1997 to 2000 found that over a period of 7.7 yrs of follow up after acute stroke, 92% patients had below normal Vitamin D levels. They suggested a definitelink between acute ischaemic stroke and Vitamin D.

The Northern Manhattan study[13] showed low vitamin D was significantly associated with increased intimal media thickness and carotid plaques in cardio embolic stroke. Vitamin D deficiency caused a dysregulation in inflammatory response and reduces neuroprotective factors like Insulin Growth Factor-1(IGF-1). Vitamin D might promote neuroplastic changes that may in turn improve clinical recovery. Since vitamin D can cross blood brain barrier and Vitamin D Receptors (VDR) are identified in brain, it also exerts antithrombotic and neuroprotective actions. **Prabhakar P et al**., found that genetic variants in VDR gene was associated with an increased risk for stroke in vitamin D deficient persons[14]. **Daubail et al**[15] suggested that beyond being a risk factor for stroke, it has been shown in 386 stroke patients, that low 25(OH) D levels at hospital admission are associated with stroke severity, as well as with poor early functional outcomes. Yarlagadda et al. also found significant improvement in the stroke recovery following correction of vitamin D levels[16]. This study has demonstrated significant improvement in disability in

both hemorrhagic and ischaemic stroke cases with normalization of the serum vitamin D level, following supplementation.

Conclusion

Multiple literature and articles have suggested the role of Vitamin D deficiency of having deleterious effects on both modifiable as well as non-modifiable risk factors.[8,9,10] Vitamin D has a number of pleiotropic effects on modifiable risk factors like Diabetes mellitus, hypertension, atherosclerosis, and many recent clinical trials conducted have provedthe neuroprotection offered by Vitamin D and its role in preventing ischaemic stroke. Following supplementation, the serum vitamin D level was found to be normalised, resulting in considerable reduction in disability in both hemorrhagic and ischemic stroke cases. Hence ,vitamin D deficiency may have a role in the development of ischemic stroke, and with intervention resulting in a significant improvement in disability and a better prognosis.

As Vitamin D deficiency is easy to screen for and inexpensive to treat, screening forit may be done routinely in all stroke cases.

STRENGTH AND LIMITATION

This study only used Scandinavian Stroke Scale , however alternative clinical assay methods,study with larger sample size and multi- center studies may be done to further substantiate these findings.

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